

mopressin use causes immediate improvement in 70% of enuretic children; relapse rates are lower than with the use of imipramine but higher than with bed-wetting alarms.

Secondary regressive enuresis responds best to crisis intervention to help the child and family cope with the identified stress that triggered the bed-wetting episode. Counseling as to the transient nature of the bed-wetting problem may prevent a more serious maladaptive response.

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## Treatment-Resistant Depression

THE BEST ESTIMATE IS THAT about 20% of depressed patients do not respond adequately to treatment. As the debilitating effects of depressive disorders on patients and their families become more apparent, it is important to develop effective pharmacologic strategies for patients whose depressions are resistant to treatment. Physicians have been hampered, however, by a lack of consensus in defining treatment resistance. It is clear that treatment intolerance—the inability to tolerate one or more antidepressant agents in sufficient doses to effect a response—needs to be distinguished from true treatment resistance. Beyond that, whether treatment resistance should be defined by a level of symptoms for a certain period of time or by a failure to respond to a number (but how many?) of antidepressant drugs at specified doses or plasma concentrations is still debated. Similarly, some authors have suggested that patients not be called treatment resistant until they have had a trial of electroconvulsive therapy, and others see electroconvulsive therapy as a strategy for patients already defined as treatment resistant.

Among patient characteristics that may predict treatment resistance, the presence of other concomitant disorders is the most important. Patients who both are depressed and have drug or alcohol abuse, severe personality disorders, or active significant medical illness have lower response rates to antidepressant treatments.

Although there are a variety of creative pharmacologic strategies for treating refractory depressions, the most important recommendations involve using the more common treatments correctly. As an example, patients should not be considered treatment resistant until they have had a trial of one tricyclic antidepressant at a dosage level of imipramine hydrochloride, 300 mg per day, or its equivalent for at least six weeks. With some antidepressants, determining trough serum concentrations of the tricyclic prescribed (the blood specimen to be drawn in the morning after nighttime dosing) and adjusting the dose according to the serum level will further enhance the adequacy of treatment. A substantial number of patients referred to as treatment resistant will not meet even this first criterion because many clinicians stop an antidepressant medication after three or four weeks of treatment, a strategy that will decrease response rates by as much as 25%.

Patients who have not responded to an adequate trial of one tricyclic antidepressant should be treated using any one

(or all four, if no response is seen) of the following strategies: adjunctive medications such as lithium carbonate added to the tricyclic regimen; switch to a cyclic antidepressant of a different class, such as fluoxetine; switch to a monoamine oxidase inhibitor antidepressant (this is probably the most underused effective strategy); or electroconvulsive therapy (for more severely depressed patients). For those patients treated with fluoxetine first, the tricyclic antidepressant would simply be substituted in its place.

Only if these basic strategies fail should the more unusual therapies, such as stimulants, combined tricyclic and monoamine oxidase inhibitor antidepressants, combined fluoxetine and tricyclics, or the anticonvulsants be tried.

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## Antidepressant Treatment in Patients With Heart Disease

THE GROWING RECOGNITION that substantial medical morbidity and mortality are associated with depression has led clinicians to treat depression in patients with coexisting serious medical disorders if it can be done safely. Because cardiac toxicity of antidepressant treatment may be the most serious concern for clinicians, it is important to review recent advances that have increased the safety of treating depression in patients with heart disease.

The most serious complication requiring caution is a conduction disturbance, especially left bundle branch block or hemiblock. Tricyclic antidepressant agents have a quinidine-like (class IA antiarrhythmic) effect, slowing conduction and potentially causing complete heart block. Indeed, complete heart block and arrhythmias are the probable causes of death in tricyclic overdose. The use of tricyclic antidepressants is contraindicated in the presence of left bundle branch block or hemiblock but not right bundle branch block because of the latter's small size. They may have additive toxicity with other class IA antiarrhythmic agents including quinidine, procainamide hydrochloride, and disopyramide phosphate. An additional problem is that the slowed metabolism of tricyclic antidepressants can exacerbate side effects including orthostatic hypotension. Trazodone may be given to patients with conduction disturbance with careful monitoring. The same may be true for fluoxetine, bupropion hydrochloride, monoamine oxidase inhibitors, and psychostimulants (methylphenidate and others).

The use of tricyclic antidepressants is generally safe in patients with ventricular ectopy because of their quinidine-like antiarrhythmic actions. In contrast, trazodone may exacerbate preexisting ventricular arrhythmias for unknown reasons. Until further research is done on this problem, trazodone should generally not be used in this context.

Antidepressant therapy is generally safe in patients with diminished cardiac contractility, as these medications do not appear to have a negative inotropic effect. Patients with ejec-

tion fractions at or below 20%, however, should be carefully monitored as a precautionary measure.

Two new antidepressants, fluoxetine and bupropion, appear to have a decreased potential for cardiotoxicity. To date, no reports of cardiotoxicity with the use of these medications have appeared in the literature. It should be noted that pre-marketing trials have been carried out on depressed patients with normal hearts, so the safety of these medications in patients with organic heart disease remains to be determined.

The safest antidepressant treatment in depressed patients with serious heart disease is electroconvulsive therapy. Although heart rate and blood pressure increase considerably during the first few minutes following the electrical stimulus using standard anesthetic techniques, creating a potential danger for a patient with a vulnerable myocardium, electroconvulsive therapy has been shown to induce only a minimal rise in these variables with the use of intravenous labetalol hydrochloride or trimethaphan camsylate (Arfonad) at the time of anesthesia induction.

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### Obsessive-Compulsive Disorder

OBSESSIVE-COMPULSIVE DISORDER had, until recently, almost always been resistant to treatment. Selective serotonergic antidepressants and behavioral therapy techniques now allow these disorders to be treated successfully.

Several double-blind placebo-controlled trials have shown fluoxetine hydrochloride (Prozac), fluvoxamine, clomipramine hydrochloride (Anafranil), and buspirone hydrochloride (BuSpar) to be effective medications. About 70% to 80% of the patients in these trials had a 45% to 55% decrease in their symptoms. In clinical terms, this meant that a patient who had spent every hour of every day locked into the performance of meaningless rituals was, after treatment, having only occasional (about once an hour) obsessive thoughts and was usually able to resist performing a compulsive ritual without an excruciating increase in anxiety. Most patients felt treatment had reduced symptoms to the point that they no longer interfered in their social or occupational functioning.

The most effective agents currently available are fluoxetine and clomipramine. The key to effective treatment with these drugs is to use a dosage schedule for a sufficient period before deciding whether a patient is treatment responsive. With clomipramine, this means using an average oral dosage of 200 mg per day (therapeutic range, 100 to 250 mg) for at least eight weeks. Patients may show little or no therapeutic response at six weeks, yet go into relative remission at eight weeks. Treatment begins at 25 mg per day and increases by 25 mg every three days, leveling off at 200 mg per day. In patients prone to panic attacks, an initial dose of 10 mg per day is used to lower the risk of inducing panic or excessive anxiety.

The dosing strategy with fluoxetine is somewhat differ-

ent. A wide range of oral doses has been reported to be effective. Consequently, most regimens should be started at 20 mg per day, increasing the dose by 20 mg every six weeks. In rare instances, the dosage may be pushed to as high as 100 mg per day, but usually 40 mg per day is a therapeutic dose.

In cases refractory to treatment, even after the addition of behavioral therapy, a variety of adjunctive and combination treatments may be used, including buspirone, lithium carbonate, monoamine oxidase inhibitors, trazodone hydrochloride, alprazolam, and fenfluramine hydrochloride. There is some evidence that buspirone may be an effective agent alone at doses averaging 60 mg per day. Nevertheless, a subgroup of patients with classical obsessive-compulsive disorders, who are suffering from neither schizophrenia nor personality disorders, remain refractory to treatment. For this subgroup, a neurosurgical procedure, limbic leukotomy, has at times proved effective.

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### Brain Imaging and Neurodevelopmental Psychiatry

NEURODEVELOPMENTAL PSYCHIATRY is gaining increasing recognition as an important theoretic approach to understanding the cause of many serious psychiatric disorders. In the past, investigators focused primarily on psychological, environmental, and genetic factors to explain psychiatric disturbance. The recent development of neuroimaging technologies for in vivo investigation has expanded knowledge of the neuropathology and physiology in such disturbances as schizophrenia, affective disorders, autism, obsessive-compulsive disorder, and attention-deficit disorder. Many of these findings confirm the presence of neuropathology that developed before the onset of the disorder.

Modalities used to image the brain include computed tomography, magnetic resonance imaging and spectroscopy, computed encephalography, positron emission tomography, and single photon-emission computed tomography. Of these neuroimaging techniques, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy are uniquely suited to study structural, physiologic, and developmental brain abnormalities in children because they involve no ionizing radiation or radioactive isotopes and have been shown to have no biologic hazards at currently used field strengths. Magnetic resonance imaging offers superior grey-white matter delineation and excellent visualizations of midline structures. As an example, MRI studies of autistic children show posterior fossae abnormalities (cerebellum, fourth ventricle, and brain stem) compared with normal controls.

Neuroimaging has been particularly useful in the study of schizophrenia. An increasing number of studies find abnormal brain structure and function in adult schizophrenic patients compared with normal controls. These abnormalities include a larger ventricle to brain ratio; enlargement of the